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Alterations of skeletal muscle microcirculation detected by blood oxygenation level-dependent MRI in a patient with granulomatosis with polyangiitis

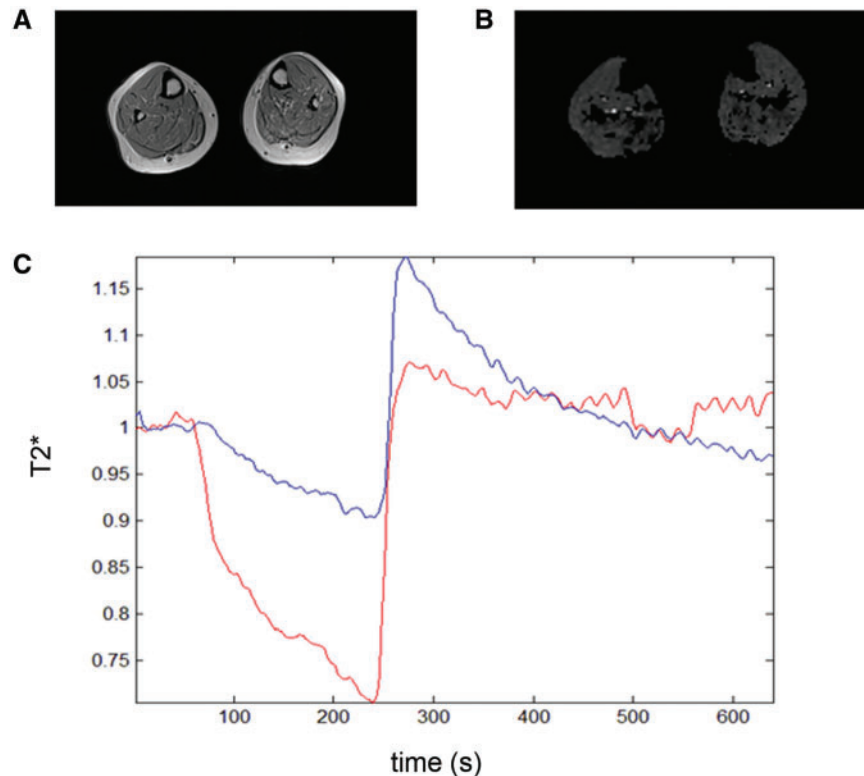
SIR, Granulomatosis with polyangiitis (GPA) is a small vessel vasculitis that is associated with cardiovascular disease, which mainly determines the prognosis of GPA patients [1, 2]. Contradictory evidence has been published regarding accelerated atherosclerosis in GPA, which might cause cardiovascular morbidity [3, 4]. Blood oxygenation level-dependent (BOLD) MRI of skeletal muscle has become a valuable tool for the assessment of vascular pathologies such as atherosclerosis, diabetes mellitus and chronic compartment syndrome [5–7]. T2*-weighted MR signal of gradient-echo echo-planar imaging (EPI) sequences is sensitive to changes of oxyhaemoglobin concentration in small pre- and post-capillary vessels [8].

Here we present a case of a 73-year-old female GPA patient who was treated in our rheumatology clinic owing to severe myalgias. She had a 7-year history of GPA with nasopharyngeal symptoms, haemoptysis, arthritis, dysesthesias and renal involvement. During her actual admission, laboratory tests revealed leucopenia of 2.6/nl (reference range 3.5–10.0/nl), lymphopenia of 0.21/nl (0.9–3.3/nl), haematocrit 0.38/l (0.36–0.46/l), CRP 0.4 mg/l (<10 mg/l), BSG 10 mm/h (0–28 mm/h), ANCA 1:20 (<1:20), anti-MPO <2.5 U/ml (<5 U/ml) and anti-PR3 6 U/ml (<5 U/ml). Her blood pressure was 130/70 mmHg. She had no history of hypertension, diabetes mellitus or hyperlipidaemia. Her peripheral pulse status was normal and she never suffered from claudication. Recent maintenance immunosuppressive medication consisted of 150 mg azathioprine and 10 mg prednisone daily. MRI measurements were indicated owing to severe myalgias of both legs and performed on a 3.0-T scanner (Verio, Siemens Medical Solutions, Erlangen, Germany). Informed consent was obtained, and the study was approved by the local ethics committee (Ethikkommission beider Basel). A T2*-weighted sequence revealed no signs of local inflammatory activity of the calves. For BOLD imaging, a healthy female volunteer controlled for age, BMI and physical activity served as control after providing consent. A multi-echo gradient-echo EPI sequence with fat suppression was used with a cuff compression paradigm as previously described [5, 9, 10]. Briefly, BOLD imaging was performed during the

last minute of a 300 s resting period, 180 s of ischaemia and 400 s of reactive hyperaemia. Four axial slices (thickness 5 mm, gap 2.5 mm) were positioned in the upper calf. With each excitation, four echo images with increasing effective echo times were acquired. Inflow (initial signal intensity, I_0) and oxygenation (susceptibility, $T2^*$) effects were separated by a pixel-by-pixel least-square fit of a monoexponential decay to the signal intensities at the four different echo times (TE_{1-4} of 9.3, 20.1, 31.0 and 41.5 ms) according to $S(I_0, T2^*) = I_0 \exp(-TE_{1-4}/T2^*)$. $T2^*$ maps were computed, supplemented with T1-reference images and ROIs placed in the soleus, gastrocnemius and peroneus, excluding pixels of bones and vessels (Fig. 1).

- (i) Absolute baseline $T2^*$ values were comparable between the two individuals (patient 21.6 ms, control 21.1 ms).
- (ii) Absolute and relative minimum ischaemic $T2^*$ values ($T2^*_{\min}$) were substantially lower in the GPA patient (15.3 ms, –29.4%) than in the control (19.7 ms, –9.5%).
- (iii) Relative $T2^*$ decline after cuff compression [ischaemic declining slope (IDS)] was significantly steeper in the GPA patient, when compared with the healthy volunteer (–4.1%/ms vs –1.0%/ms).
- (iv) Absolute and relative $T2^*$ peak values during reactive hyperaemia ($T2^*_{\max}$) were strongly reduced in the patient (23.6 ms, +7.0% vs 25.0 ms, +18.4%).
- (v) Time to peak value (TTP), reflecting the time from cuff deflation to $T2^*_{\max}$, was similar between the two subjects (32 s vs 34 s).
- (vi) $T2^*$ end value (EV, reflecting medium $T2^*$ during the last 10 s of measurement) was higher in the GPA patient compared with the control.

These findings strongly suggest major perturbations of skeletal muscle microcirculation in this GPA patient, revealed by skeletal muscle BOLD MRI. The lower $T2^*_{\min}$ value in the patient might be explained by increased oxygen consumption as control and patient showed comparable baseline absolute $T2^*$ values, and the IDS absolute value was substantially higher in the patient. This might be a compensatory mechanism for chronic hypoxic conditions in patients with GPA. $T2^*_{\max}$ decrease could be explained by reduced blood flow in skeletal muscle microvessels, owing to small vessel vasculitis. The underlying mechanisms of the detected BOLD alterations have to be interpreted with care owing to other $T2^*$ influencing factors such as blood volume, haematocrit, functional vascular status and metabolic changes [5, 7]. Owing to the lack of reference methods for the measurement of perfusion or oxygenation, our findings remain mostly descriptive. However, the measured BOLD response in GPA is different from previous results in patients with atherosclerosis that showed diminished ischaemic $T2^*$ decline and a prolonged TTP [5, 10]. This may indicate that other mechanisms besides accelerated atherosclerosis play an important role in the pathogenesis of skeletal muscle microcirculation alterations in GPA. Of course,

Fig. 1 BOLD MRI in a patient with GPA.

Anatomical reference image (T1) of the examined upper calf region (**A**) and the corresponding T2* maps (**B**). T2* time courses (**C**) of the left leg in the patient with GPA (red) and the healthy volunteer (blue). A steeper signal decline to a significantly lower T2*_{min} could be detected in the GPA patient. After cuff deflation, T2*_{max} was extensively reduced in the patient and signal decline was slower than in the control.

further studies with larger patient collectives are warranted to elucidate the underlying mechanisms of the described BOLD signal alterations in GPA.

Rheumatology key message

- Alterations of skeletal muscle microcirculation in GPA can be revealed by BOLD MRI.

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Vasculitis following HPV immunization

Sir, we report two cases of vasculitis following HPV immunization, which has not previously been described. Case 1, a 15-year-old girl, presented with three small purpuric lesions on the lower left leg 3 days after the second dose of the HPV vaccine. These progressed over the next 2 weeks to a florid purpuric rash affecting the lower limbs, buttocks and extensor surfaces of both elbows. She was afebrile, with no abdominal pain or arthritis; blood pressure was normal. Urinalysis showed +++ of blood but no protein or nitrates.

A diagnosis of probable Henoch–Schönlein purpura (HSP) was made. Two weeks later she re-presented with extensive generalized vasculitic rash, soft tissue swellings of both ankles and forearms, arthralgia, lethargy and epistaxis. Laboratory tests were normal (CRP <5 mg/l, ESR 25 mm/h). Full autoantibody screen was negative; complement (C3, C4) and serum immunoglobulins were normal. Skin biopsy showed a mild perivascular lymphocytic inflammatory cell infiltrate and occasional eosinophil interstitial infiltrate. The swellings and cutaneous vasculitis initially improved with oral prednisolone and antibiotics but deteriorated dramatically as CSs were discontinued. Ten weeks after the initial presentation, the vasculitic rash was re-biopsied, revealing a leukocytoclastic vasculitis (LV); immunofluorescence was negative for IgA deposition. Treatment with prednisolone (0.5 mg/kg/day) and colchicine (1500 µg/day) was started. Azathioprine was subsequently added as an additional steroid-sparing

agent, which led to resolution of the vasculitis and successful steroid taper.

Case 2 was diagnosed with HSP at the age of 13 years with typical cutaneous vasculitis, abdominal pain, arthralgia and microscopic haematuria. Laboratory tests including renal function, inflammatory parameters and full autoimmune workup were normal. IgA was elevated at 3.54 g/l (0.8–2.8). Infectious workup was negative. Over the next 2 years there was gradual resolution with recurrent vasculitic skin rash lasting for a few days mainly after intercurrent infections. Aged 15 years, with the vasculitis in remission, the first dose of the HPV bivalent vaccine was given. Three days later she had a severe flare of cutaneous vasculitis. Laboratory tests were as previously documented. Skin biopsy showed endothelial cell hyperplasia and neutrophil infiltration into the vessels within the dermis, compatible with acute cutaneous vasculitis. Immunofluorescence for IgA, IgG, IgM, C1q, C3 and fibrin was negative and consistent with cutaneous LV [1].

To the best of our knowledge, these are the first reports of vasculitis associated with the HPV vaccine. Both cases presented with a small-size vessel vasculitis predominantly affecting the skin soon after HPV vaccination, the first being a *de novo* isolated cutaneous LV and the second a vasculitis recurrence. Immunization with HPV vaccine has the potential to decrease the global morbidity and mortality of HPV-related disease, including cervical cancer, and thus represents a major breakthrough in medicine [2]. As HPV 16 and 18 are involved in the pathogenesis of 70–75% of all cases of invasive cervical cancer, vaccination in this context offers an effective means of primary cancer prevention [3] and is only the second vaccine that has been licensed with this indication [4].

Overall the balance between the risks and benefits of the HPV vaccine is overwhelmingly positive. A recently published pooled analysis of 11 clinical trials showed no significant differences between the vaccine and the control group regarding severe side effects or the development of chronic illnesses including autoimmune diseases [5].

LV is the most frequent form of vasculitis affecting the skin, involving small vessels but particularly post-capillary venules. In many cases, LV is caused by large immune complexes deposited at the vessel wall, which can be either IgA (as in HSP) or contain IgM or IgG. LV can also be secondary to ANCA-associated vasculitis and can occur without immune complex deposition [6]. The failure to demonstrate IgA deposits by immunofluorescence on skin biopsy makes these cases better classified as hypersensitivity cutaneous LV despite the initial presumptive clinical diagnosis of HSP [7].

Several infectious agents and drugs have been inconclusively identified as possible infective triggers of hypersensitivity LV. In our reported cases, there was no history of preceding infection, and the strong temporal relationship between the administration of the bivalent HPV vaccine and the development of vasculitis was notable.